ANAPHARM

September 30, 1999

Dockets Management Branch (HFA-305)
Food and Drug Administration,
5630 Fishers Lane, rm. 1061,
Rockville, MD 20852

Dear Sir or Madam:

I would like to give comments regarding the two new draft guidances that have been issued by CDER on Bioavailability (BA), and Bioequivalence (BE) studies, dated August, 1999.

First, I would like to give some general feedbacks before getting into the specific aspects of both guidances.

The concept of Individual Bioequivalence (IBE) has been raised by a purely statistical hypothesis, suggesting that current Average Bioequivalence (ABE) approach does address prescribility, but not swithability. The IBE approach is thought to provide a better estimation of the bioequivalence of two products by comparing not only the means, but also the within formulation variance, and subject by formulation interaction (S*F). I have suggested that a S*F value 0.15 or higher may present some concern. However, I would like to stress that S*F value is purely a statistical term with no direct clinical correlation. Moreover, since S*F is a component of the residual error in a standard two-way crossover study, drugs exhibiting large degree of intraindividual variability (e.g. complex formulation, highly variable drugs, substrates for CYP3A4 and PgP) are more likely to exhibit this problem.

A pilot period study of two years aimed at establishing whether this hypothesis is real will be more effective, if applied on a subset of drugs. Therefore, I agree with the recommendation of the expert panel (blue ribbon panel). I don't think that drugs with low variability (i.e. intraCV less than 15%) should be studied in a replicate study design since they are highly unlikely to have subject by formulation interaction. Moreover, since narrow therapeutic index drugs have low variability, I would suggest to only recommend performing replicate study design when variability is more than 10%.

I was also present at both conferences in Montreal (August 30- Sept.1 , 1999), and in Washington (Sept.23, 1999). The only two studies cited to support the rationale for undertaking such a drastic approach were not convincing: The methylphenidate example could have been predicted from in vitro dissolution data; the levothyroxine data was also predictable from in vitro dissolution data. Moreover, if we were to apply the guidance for all drugs as it is proposed, we would not have seen the same results for levothyroxine since the study was conducted at steady-states on patients and the subject by formulation interaction observed was shown on a phannacodynamic endpoint.

In the next two sections, I will comments on both guidances separately.

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Average, Population, and Individual Approaches to Establishing Bioequivalence.

Population approach: There is no advantage in using population approach compared to the widely accepted method (ABE). The only difference is in the scaling, and comparison of variance. However, it appears that despite crossover study design, total variance will be compared instead of the intrasubject variance. In fact, the guidance proposes to estimate each source of variance, then sum them to obtain the total variance. Then, why conducting a study in a crossover fashion if you are not interested in the within subject variance? In addition, we already know that the between subject variability is much larger than the within subject variance. As such, drugs with large between subjects variance may get approved due to scaling.

Therefore, I propose to not use population BE, unless the study is conducted in parallel.

IBE approach: During the interim pilot period of two years, if a replicate study design is used, it is unclear whether the decision of bioequivalence will be based on ABE, IBE, or both. If bioequivalence should be met for ABE, then studies should be powered from standard two-way crossover study, unless scaling was allowed. This needs to be defined.

For narrow therapeutic index drugs, the guidance proposes to scale, regardless of the variability. This recommendation has no scientific basis. In fact, real data (not simulation) were presented in Montreal demonstrating that scaling for drugs (NTI) with low variability, is too restrictive and may not allow any generics to be approved, due to the nature of the aggregate criteria (i.e., scaling with an extremely low value). instead, I recommend for drugs with low variability (i.e., intraCV less than 15%, perhaps 10% for NTI) to use constant scaling.

Instead of scaling for NTI, I recommend restricting the criteria *which will make more sense (i.e., e=0, and 90% CI or 95% CI within 90-1 11% for ABE).*

ABE approach:

I agree with the proposal in Montreal and Washington suggesting to allow scaling of ABE for highly variable drugs. The guidance should provide the method to be used.

BA and BE Studies for Orally Administered Drug Products- General Considerations.

In general, I agree with the proposition in this draft, except for requiring replicate study design for all drugs that do not fit the category. I will be best, I think, to state which drugs should be studied in a replicate study design.

Specific comments:

III- Methods to Document BA, and BE.

A. Pharmacokinetic studies

4. Replicate study designs. The guidance mentioned to avoid any confusion and numerous communications with the agency. I would state which drugs, or types of formulations should be studied in a replicate study design.

5. Study Population: There is no longer any superior limit of age, or restriction in terms of body weight. I agree with this, especially when the study is conducted crossover. However, it may be hard to enroll healthy elderly subjects with no concomitant meds ,or diseases. In addition, I would not make mandatory to enroll different ethnic groups as we may exclude several subjects due to mixed ethnicity. For example, how would you classify a second generation Asian (paternal sides, and American African (maternal side)? I would rather propose to enroll subjects regardless of ethnicity.

B. No Comment

C. IR: Capsules of Tablets.

1. **General recommendations:** I disagree with the statement regarding scaling for NTI because of the reasons stated above.

VI- Special Topics:

B. Moieties to Be Measured

1. Parent Drug versus Metabolites.

For BA studies, metabolites, and parent drugs should be measured, whereas for BE studies, only the active moieties, and/or active ingredient are recommended.

However, the paragraph which talks about the formation in the gut should be better explained, and examples should be provided to illustrate this problem. If both the gut and liver were responsible for metabolites formation (e.g. CYP3A4 substrates), should the active metabolites also be measured?

I hope that these comments are useful, and look forward with the agency's final guidance.

P.S: I remain available should you have any comments, questions, or other items you would like to discuss.

Sincerely,

Eric Masson, Pharm.D.

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